Multiorgan *Streptococcus milleri* Abscesses During FOLFIRINOX Chemotherapy in a Patient With Metastatic Pancreatic Cancer

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CASE REPORT

A 66-year-old active, healthy man presented with 1 month of abdominal bloating, nausea, sharp left upper quadrant pain (LUQ), loss of appetite due to early satiety, and a 7-lb weight loss. He denied diarrhea, steatorrhea, pruritus, or jaundice. There was no history of diabetes or pancreatitis and no family history of cancer. He had never smoked and had alcohol only occasionally, with no prior heavy alcohol use. His medical history was notable for degenerative joint disease, paroxysmal atrial tachycardia, and hyperlipidemia. These were treated with the medications ibuprofen, flecainide, metoprolol tartrate, and simvastatin. His examination showed mild LUQ tenderness and guarding. Presenting labs were within normal limits. A computed tomographic (CT) scan showed a 6.6 × 5.7-cm mass in the pancreatic tail extending into the left adrenal gland, lesser sac, and splenic vein (Figure 1). There were multiple, small liver hypodensities of indeterminate nature. A diagnostic laparoscopy revealed peritoneal carcinomatosis, and a biopsy confirmed adenocarcinoma consistent with a pancreatic primary.

FOLFORINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) therapy was initiated for stage IV metastatic pancreatic cancer. The patient developed gastrointestinal (GI) toxicity and neutropenia requiring a 25% dose reduction after 2 cycles. Pegfilgrastim (Neupogen) was added to cycle 3 and prevented any further episodes of neutropenia. No oral lesions were noted at any time during treatment. One week after cycle 4, the patient experienced 2 episodes of fever resulting in a visit to the emergency department, but no clinical, radiologic (chest X-ray), or laboratory evidence of infection or neutropenia was found. A repeat CT scan after cycle 4 showed a 20–30% regression in the pancreatic mass, stable liver lesions, and peripheral splenic hypodensities consistent with splenic infarcts. After cycle 7 of FOLFIRINOX, the patient presented with confusion, homonymous hemianopsia, and expressive aphasia. Urgent brain magnetic resonance imaging (MRI) revealed ring enhancing lesions in the left occipital region with surrounding vasogenic edema consistent with abscesses (Figure 2). The patient was taken to the operating room and neurosurgical drainage revealed purulent fluid. Cultures grew *Streptococcus milleri* (also known as *S. anginosis*). Fungal and anaerobic cultures were negative, as was polymerase chain reaction (PCR), for *Toxoplasmosis gondii*. The patient was treated with vancomycin, ceftriaxone, and metronidazole. A third CT revealed additional abscesses in the liver and spleen (Figure 3). An interval increase in the size of the pancreatic tail mass with invasion into the adjacent stomach wall and spleen and new ascending colon wall thickening were also noted. Drainage of the splenic fluid confirmed *S. milleri*, and liver fluid also revealed Gram-positive cocci consistent with *S. milleri*. Blood cultures remained negative throughout. A transthoracic echocardiogram with bubble study was negative for endocarditis, and there was no shunt. The patient developed intermittent seizures and continued neurological deterioration, despite antibiotic therapy. He was admitted to hospice care and died 9 months after diagnosis.

DISCUSSION

Metastatic pancreatic cancer is a devastating disease with a 5-year survival of just 2%. Gemcitabine-based therapy has been the cornerstone of treatment since the 1990s. However in 2011, results of a randomized, multicenter trial revealed markedly improved response rates and improved survival with FOLFIRINOX, when compared to single-agent gemcitabine therapy.[1] However, FOLFIRINOX was associated with higher rates of neutropenia, febrile neutropenia, diarrhea, and sensory neuropathy than gemcitabine. At the American Society of Clinical Oncology (ASCO) 2010 meeting, where the data were presented, discussant Margaret Tempero[2] emphasized that the toxicity of the regimen was very troubling and that FOLFORINOX may only be a good fit in "patients who are less than 76 years old [and] have good performance status (ECOG [Eastern Cooperative Oncology Group] 0 or 1), no cardiac ischemia, and normal or near normal bilirubin levels." She noted that the typical patient with pancreatic cancer does not fit this description. Nevertheless, she and others recognized this therapy as ground-breaking, and she concluded that "this is not a contest about what is best for everyone—it is very good to have options." FOLFIRINOX has now become an accepted standard of care for metastatic pancreatic cancer, but its use is limited to patients who can tolerate the increased toxicity profile.[1–4] A better understanding of adverse effects from continued clinical use can inform clinicians who are monitoring patients who receive this therapy. Péron et al,[5] described a case of opportunistic pulmonary coinfection with *Pneumocystis jirovecii* and invasive aspergillosis during FOLFIRINOX therapy for pancreatic adenocarcinoma with liver metastasis. The patient was a 47-year-old nonsmoker, did not have the human immunodeficiency virus (HIV), had normal CD4 and CD8 counts,

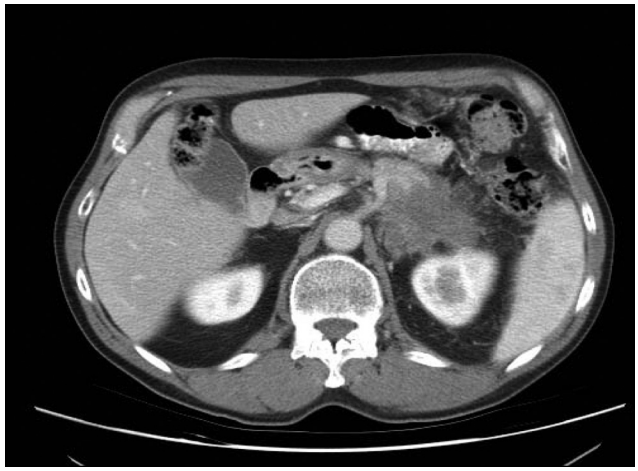

Figure 1. Contrast-enhanced staging CT of the chest, abdomen, and pelvis showing a 6.6 × 5.7-cm irregular mass in the tail of the pancreas.

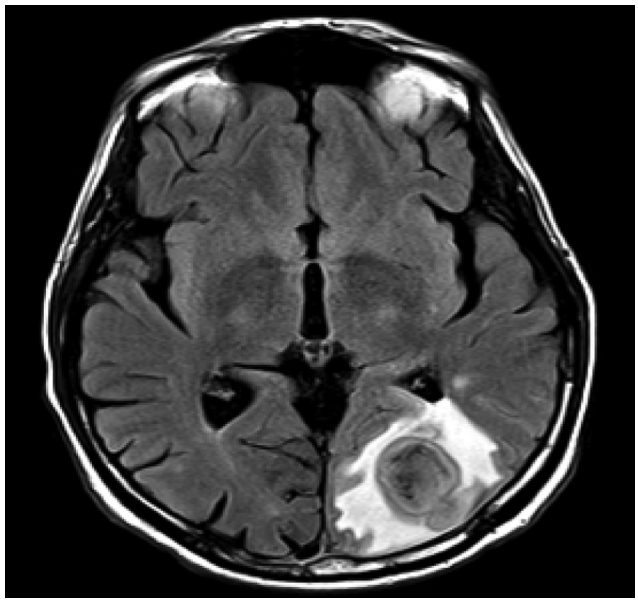

Figure 2. A brain MRI, with and without contrast, revealed a ring enhancing lesion and surrounding vasogenic edema consistent with an abscess.

had an ECOG score of 1, and had received granulocyte colony-stimulating factor, but still developed febrile neutropenia while on FOLFIRINOX. They noted that these infections rarely occur in patients in treatment for nonpulmonary solid tumors. Fortunately, the patient responded to treatment. In the current case study, we describe a previously unreported adverse effect of disseminated abscess formation by infection with *S. milleri* during therapy with FOLFIRINOX.

S. milleri, a stealthy and virulent pathogen

S. milleri was the name given in the 1950s to members of the Viridans streptococcal anginosus species group.[6–8] It consists of three related species: *S. anginosus*, *S. constellatus*, and *S. intermedius*. Phenotypic characteristics readily identify streptococcal strains as members of the *S. milleri* group (Figure 4), but accurate identification to the subspecies level is more challenging. Many strains produce diacetyl, imparting a buttery odor to cultures. *S.*

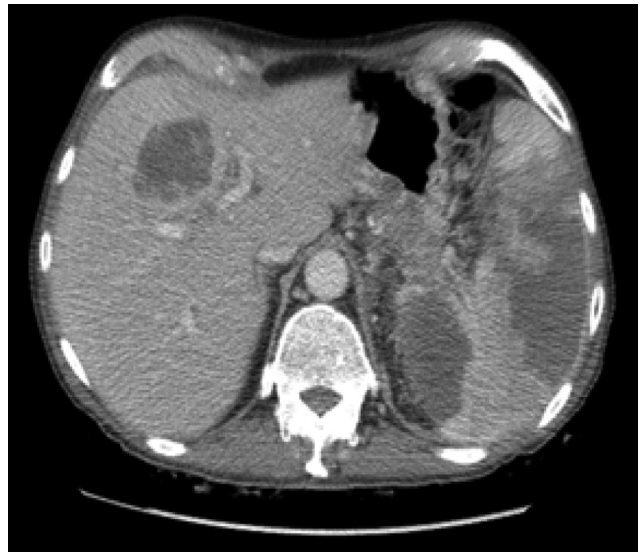

Figure 3. CT of the chest and abdomen with contrast: spleen and liver abscesses.

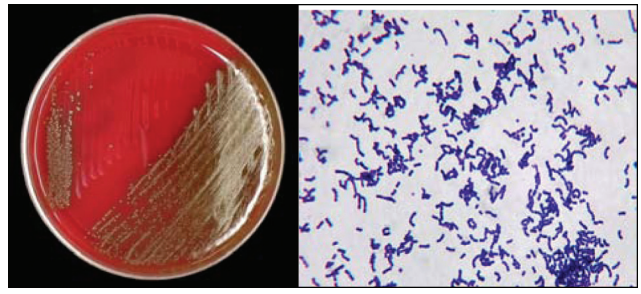

Figure 4. *S. anginosus* (*S. milleri*) plated from abdominal fluid. Photo taken by Yuri E. Amatnieks, HBSc, MLT. Used with permission. http://thunderhouse4-yuri.blogspot.com/2010/12/streptococcus-anginosus-group.html.

milleri organisms are usually harmless members of normal oropharyngeal and GI flora. Strains have adhesins to facilitate colonization and hydrolytic enzymes capable of destroying host tissue, and *S. intermedius* strains produce intermedilysin, a cytolytic toxin, but their pathogenic mechanisms are not well described. *S. milleri* can often be isolated along with anaerobic bacteria; this association is thought to be synergistic, causing increased virulence.

S. milleri have a propensity to cause pyogenic abscesses that can be challenging to treat. Cases of *S. milleri* infections have been reported in individual organs—the central nervous system (CNS),[9,10] lung,[11] heart, and liver[12] (Figure 5), and skin—but it is unusual to find disseminated infection with abscesses in 3 separate organs simultaneously. The patient in this case did not have any oral lesions or dental surgery throughout his treatment, which suggests that the gut was the likely source. We postulate that the typical side effects of FOLFIRINOX therapy (ie, neutropenia and GI mucosal inflammation and disruption), allowed for translocation of normal gut flora and subsequent bacteremia, leading to seeding in the patient's brain, spleen, and liver. Perhaps the fevers he experienced after cycle 4 were a harbinger of bacteremia and occurred at a time that was coincident with documented tumor shrinkage on imaging. Physicians caring for patients receiving FOLFIRINOX therapy must remain vigilant for untoward toxicity from this therapy. Careful patient assessment in the clinic is warranted with each new

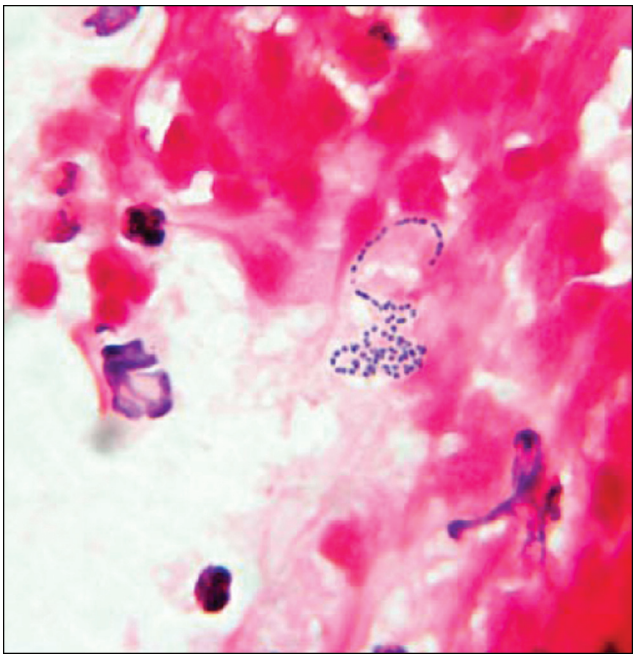

Figure 5. *S. anginosus* (*S. milleri*) in a liver aspirate: Gram-positive cocci in pairs and chains. Photo taken by Yuri E. Amatnieks, HBSc, MLT. Used with permission. http://thunderhouse4-yuri.blogspot.com/2010/12/streptococcus-anginosus-group.html.

cycle of therapy, with any new sign or symptom viewed with a high index of suspicion.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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